THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES

JUNE, 1916

---

## ORIGINAL ARTICLES

# THE RESPIRATION CALORIMETER IN CLINICAL MEDICINE.*

By Eugene F. Du Bois, M.D.,
NEW YORK CITY.

(From the Russell Sage Institute of Pathology in affiliation with the Second Medical Division, Bellevue Hospital, New York.)

In these days when the housewives speak in terms of calories nd the newspapers deal with vitamines it may be well for clinicians o examine once more the fundamental principles of nutrition. atients no longer demand medicines but they do expect diets, nd if they are at all up with the magazine literature, they are etter informed on the subject than the text-books which most of s studied in the medical schools. The diets which patients receive n most of our hospitals were laboriously compiled several generaions ago and modified from time to time by hospital dietitians. oods were classified according to their solidity as administered, egardless of what happened in the stomach. Details were left o the head nurse and sometimes to their probationer, and while he patient always had the veto power because he could vomit he as seldom able to initiate legislation.

The science of nutrition in disease must be founded upon experients in calorimetry and the respiratory metabolism. It may be ell at this point to state just what is meant by the term metaolism. The word in itself indicates the transformation of matter nd refers to the breaking down of foods, to their absorption, and o the building up of body tissues. The term also refers to the oxidation of food-stuffs and of body tissues, with the consequent liberation of warmth and energy. Analysis of food, urine and blood gives an incomplete picture, and it is only through a study of the gaseous exchanges in the tissues that we can study the total metabolism. There are many phrases which have the same meaning as total metabolism. Frequently it is spoken of as *the* metabolism. Sometimes it is called the total energy requirement, total food requirement or heat production, total oxidative processes or total gaseous exchange.

---

* Lecture delivered before the Harvey Society of New York, November 27, 1915.

In the years between 1892 and 1908 there was no work being done on this subject in our American hospitals, although Atwater and his successor Benedict, in Middletown were making classical experiments on normal men, and Lusk, here in New York, was making similar experiments on dogs. During this same period in Germany the respiratory metabolism was being studied in a dozen clinics and the investigators were hoping that at some time means would be found to apply the apparatus of Atwater and Benedict to the study of disease, since this alone would solve certain problems. About seven years ago, Benedict and Joslin,[1 2 3] in Boston, began to study the respiratory metabolism of diabetes, and four years ago investigation of the gaseous exchanges of typhoid patients was begun in Bellevue Hospital.[4] Shortly afterward the directors of the Russell Sage Institute of Pathology decided to turn over their funds to Professor Graham Lusk for a period of five years in order that a calorimeter might be built and maintained in Bellevue.

This respiration apparatus is perhaps the most complicated piece of machinery used in modern medicine, but the principles involved in its construction are simple. The description would seem to be a mass of technical details were it not for the fact that it illustrates beautifully the manner in which medicine is founded on physiology and physiology on physics and chemistry.

The first Atwater-Rosa[5] calorimeter in Middletown was a large chamber in which a man could lie in bed, stand up or ride a stationary bicycle. This apparatus is now in Washington, under the charge of Langworthy and Milner[6] who have made many improvements. Atwater's work, however, has been chiefly continued by Dr. F. G. Benedict,[7 8] of the Nutrition Laboratory in Boston, where great advances in the science of calorimetry have been made. Dr. H. B. Williams,[9] of New York, who constructed the small and very accurate calorimeter for Lusk at the Cornell Medical College, has added many ingenious devices. The Sage calorimeter was finished by Mr. J. A. Riche and Mr. G. F. Soderstrom,[10] in the early part of 1913. It has all the modern improvements and is especially adapted for clinical work where observations must be short. Fortunately it is situated in a room near the medical wards of the second division of Bellevue. It is next door to a small diet kitchen and metabolism ward, where three specially trained nurses weigh out the food and collect the specimens.

The calorimeter itself consists of a copper box about the size of the lower berth of a sleeping car. It contains a comfortable bed and is provided with two windows, a shelf, a telephone, a fan, a light, and a Bowles stethoscope for counting the pulse. The ordinary experiment takes about as long as a trip from New York to New London, and there is an agreeable absence of cinders. Patients, as a rule, doze from time to time or else try to work out some scheme by which they can amuse themselves without moving. After three or four hours they are rather bored by the quiet, and the observations are not prolonged beyond this time. They are allowed to turn over in bed once or twice an hour, but reading and telephoning are discouraged, since these increase the metabolism. The air in the box is fresh and pure, the patient suffers no discomfort, and objections to the procedure are very infrequent. Most of the patients are only too glad of the extra attention, and they insist that the calorimeter has a marked therapeutic value.

The apparatus has two distinct functions: (1) the physical measurement of the heat production of an individual by the method of direct calorimetry; (2) the chemical measurement of his gaseous exchanges and the calculation of the heat by the method of indirect calorimetry. Both depend on the fact that the apparatus is a closed circuit, absolutely shut off from the surrounding atmosphere in such a manner that everything eliminated by the subject is caught and measured.

None of the heat radiated from the man's body can travel through the insulating walls of the calorimeter. All is caught and measured in a stream of cold water flowing through a pipe in the top of the box. It is necessary to measure also the heat dissipated from the body in the vaporization of moisture from skin and lungs. A man loses about one-quarter of the total heat in this manner, and the 20 to 30 grams of water evaporated each hour are caught in a sulphuric acid bottle in the ventilating current. The grams of water multiplied by the factor for the latent heat of vaporization gives us the calories so eliminated. These measurements are very accurate, but it is difficult to determine how much heat a man stores in his body when his temperature rises or how much he releases from his body when his tempertaure falls. The rectal thermometer does not always tell us of the changes in the average body temperature, and an error of 0.1° C. may cause an error of 5 or 6 calories. It is for this reason that direct calorimetry is difficult when the fluctuations of temperature are great. When short periods are employed we therefore place our chief reliance on the method of indirect calorimetry.

This second method is entirely chemical; and, since it involves a different set of measurements, it serves as an excellent check on the accuracy of the results. The calorimeter is air-tight, and is connected with a series of absorbing bottles by means of a closed circuit or pipes. Air is drawn from the foot of the box by a rotary blower, passed through a bottle of strong sulphuric acid to remove the water vapor and then through weighed bottles of soda-lime and sulphuric acid, which catch the carbon dioxide. By noting the change in weights of these bottles the amounts of water and carbon dioxide removed may be determined. The air thus purified is returned to the box and is used again and again. Meanwhile the subject is consuming oxygen, and this would decrease the volume of gases within the box were it not for the fact that oxygen is automatically admitted from a weighed bomb to compensate exactly for the amount consumed. If we divide the liters of carbon dioxide produced by the liters of oxygen consumed we obtain the respiratory quotient. Knowing this and the amount of nitrogen eliminated in the urine it is possible to calculate the grams of protein, fat, and carbohydrate metabolized each hour. From their well-known heat values we can reckon out the calories produced. With the exception of a portion of the protein molecule each food-stuff is oxidized to the same end-products and with the same liberation of heat in the body as in the Liebig combustion furnace or the bomb calorimeter. The process is slower but just as complete, and there is no loss of energy.

The experimental procedure is not very complicated. A patient is given his ordinary supper in the evening. The next morning his breakfast is withheld and he is put in the calorimeter at about ten o'clock. By eleven o'clock the machine is brought into thermal equilibrium and the experiment is started. At the end of each hour the ventilating current is switched to a new set of absorbing bottles, and by one or two o'clock the observation is over. Calculations consume an hour or so more, and as soon as the urinary nitrogen is determined we have the following information in regard to the patient in hourly periods: consumption of oxygen; output of carbon dioxide; output of water and the total calories; percentage of calories furnished by protein, by fat, by carbohydrate; percentage of heat lost by vaporization, by radiation, and conduction and by storage in or loss from the body; and finally, total metabolism and its relation to the average normal figure, this total metabolism being measured by two independent methods. As may be supposed, these activities keep the three observers fairly busy, since they involve about 40 weighings, 500 temperature readings, and the writing of over 4000 figures.

The accuracy of the calorimeter is tested at regular intervals by burning known amounts of alcohol and comparing the actual findings with the theoretical. In 9 such tests the average error for heat production was 0.9 per cent., for oxygen 1.2 per cent., for carbon dioxide 0.8 per cent. The total errors are even smaller.

It is hardly necessary to point out that the results obtained with the calorimeter are due to the team work of the whole staff, including the nurses who administer the diets and the chemists who analyze food, blood, urine, etc. Those chiefly responsible for the work here presented are: Dr. Lusk, the scientific director; Mr. Gephart, Dr. Meyer, Mr. Soderstrom, Mr. Harries, Miss Magill, all of the Sage staff, and out associates, Dr. Warren Coleman, Dr. F. M. Allen, and Dr. F. W. Peabody.

There have been many types of apparatus used in the study of the respiratory metabolism in disease.[11] Unfortunately time does not permit of their description, but one cannot help mentioning by name the Pettenkofer-Voit chamber, the Zuntz-Geppert apparatus, the Benedict Unit,[12] [13] and the Paschutin calorimeter.

The main object of all investigators has been to determine the heat production of the patient while at complete rest fourteen hours or more after the last meal. This is the so-called basal metabolism, and is of interest only when compared with the figures obtained on normal individuals. Since it is impossible to measure the metabolism of many of our patients when they are entirely recovered, it is necessary to calculate what the man's metabolism would be were he normal. Here lies the most difficult problem. Controversies have raged more fiercely about the normal controls than about the pathological cases. It has been said that a man is as old as his arteries. It may also be said that a piece of research work is as good as its normal controls.

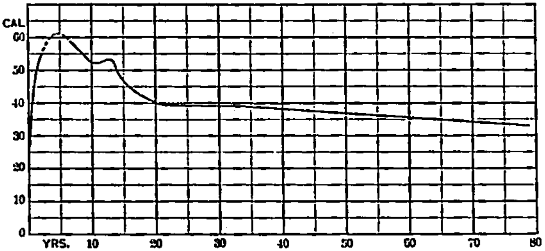
The normal controls used by investigators up to the last few years often showed a variation of 50 per cent. above or below the average. It was discouraging to run the calorimeter within an error of 1 or 2 per cent. and then compare the results with such an uncertain figure. Now this variation in the normals was largely due to the manner in which the results were expressed. If we leave the calculations, as was previously done, in the stage of cubic centimeters of carbon dioxide per kilogram of body weight there might be a large apparent variation between two men whose heat production is identical. Part of this error is eliminated if we express the results in calories, and still more eliminated if we base our calculations on surface area rather than body weight. A large man, of course, gives off more heat than a small man, but for each kilogram of body weight the small man has the higher metabolism. Rubner[14] demonstrated many years ago that the metabolism is proportional to the surface area of the body and that for each square meter of skin large men, small men, dogs, horses, and mice have about the same heat production. Just why this should be we do not know. It reminds us at once of Newton's law that the cooling of bodies is proportional to their surface area, but the metabolism does not follow this law when the external temperature is raised or lowered.

There are several formulas which allow us to calculate the surface area of a man. Meeh's[15] formula, which is proportional to the two-third power of the weight has been the standard for over a generation, and up to the last year entered into almost all the calculations. One divided the calories produced per hour by the square meters of surface area and obtained the calories per square meter per hour. Very recently the accuracy of Meeh's formula was investigated by the Sage staff. Mr. Delafield Du Bois[16] devised a method of measuring the skin area which has been applied to ten individuals of every conceivable shape. He found an average plus error of 16 per cent. in Meeh's formula and an error of 36 per cent. in fat subjects. To correct these the so-called "linear formula" was devised and also a simpler formula based on height and weight.[17]

It is interesting to group the normal controls studied in the Sage calorimeter[14] with the large number of healthy men and women studied by Benedict, Emmes, Roth and Smith in Boston,[19] [20] [21] [22] [23] and also by Palmer, Means, and Gamble.[25] If we plot the men under fifty years of age according to calories per square meter of surface area we find that all are within 15 per cent. of the averages and 86 per cent. are within 10 per cent. of the average. According to Meeh's formula thin people have an increased metabolism and fat people a very low metabolism. Using the more accurate linear formula, Means[24] [25] [26] has found the metabolism in most cases of obesity to be within normal limits, and if we recalculate the figures for groups of thin men and fat men according to their true surface area the results in the two groups are almost identical.

We can therefore feel certain that with men between the ages of twenty and fifty the metabolism of each individual is proportional to his surface area whether he be short or tall, fat or thin. We can compare all our pathological cases with the normal average basal metabolism of 34.7 calories per hour per square meter of surface according to Meeh's formula, or, better still, 39.7 per square meter according to the new so-called linear formula. The normal variation from this average is plus or minus 10 per cent. and a few apparently normal men show a variation of 15 per cent. We cannot consider the metabolism of an individual patient to be abnormal if within these limits, but if a group of patients gives an average of more than 10 per cent. from the normal base line we can feel certain that there is a pathological change in the heat production in that particular disease.

Comparisons of different persons can be made only by determining the basal metabolism. There are many factors which cause certain groups of normal individuals to depart materially from our mean figure of 39.7 calories per square meter per hour. Women give an average about 6 per cent. below this,[22] athletes are about the same distance above, as has been shown by Benedict and Smith.[21] Age causes a marked difference which will be discussed later. The metabolism seems to be higher in the afternoon than in the morning, and during profound sleep there is a drop of 5 to 20 per cent. The metabolism is 5 to 10 per cent. higher sitting upright in a chair than when lying down, but it has recently been found that the metabolism of subjects propped up comfortably in a steamer chair is a little lower than when they are lying flat in bed.[27] This throws some light on one of the many causes of the assumption of the orthopneic position by patients. It lends scientific support to the empirical observation that a lazy man is happiest with his chair tilted back and his feet on the desk.



Variation of basal metabolism with age. The curve shows the changes in the level of the heat production from birth to old age. The results are expressed in terms of calories per square meter of body surface per hour. Only male subjects were used in making the curve. The surface area was estimated by the linear formula or the comparable height-weight formula except in the case of the infants, where it was necessary to use Lissauer's formula. The normal variation from the above line is plus or minus 10 per cent. Details of this curve will be published in the Archives of Internal Medicine.

As I have said, the basal metabolism is measured fourteen hours or more after the last meal because food stimulates the metabolism. This is due to the so-called specific dynamic action of foods, and is greatest in the case of protein and least in the case of carbohydrate. The phenomena, first discovered by Rubner,[28] have been studied in great detail by Lusk,[29] using the dog calorimeter at the Cornell Medical College. He has found that the specific dynamic action of protein is due to the stimulus of the metabolism products of amino-acids acting upon cell protoplasm, and that although the preliminary cleavage products of fat and carbohydrate do not appear to be direct stimuli, yet when they are present in excess in the fluid bathing the cells, the heat production is increased. With the normal controls in the Sage calorimeter[13] a standard protein meal containing 10 grams of nitrogen causes an average increase of 12 per cent. in the five to six hours after its ingestion, and 100 grams of dextrose causes an increase of 9 per cent. These same meals have been used to test the specific dynamic action of foods in typhoid fever and exophthalmic goitre.

The curve showing the effect of age on heat production is of special interest. Magnus-Levy and Falk[30] demonstrated that the metabolism was high in childhood and low in old age, and no one will doubt this who has compared the amounts of food consumed by children and by their grandparents. We have now at our command a large number of observations made at all ages except the period between the second and sixth years. The reason for this gap is apparent. The shortest experimental period is ten minutes, and normal children of this age are never quiet for this length of time. The metabolism of infants has been studied by Howland,[31] Benedict and Talbot,[32 33 34] by Murlin and Hoobler,[35] Bailey and Murlin[36] and others. Eight boy scouts, not long ago, were studied in the Sage calorimeter[37] and made to keep quiet by a system of fines and rewards. If we tabulate these with all the other children and adults we can trace a curve which shows the heat production per square meter of surface at different ages, and compare it with the average adult figure. During the first few weeks of life the metabolism is very low, after which it rises rapidly until at the end of the first year it is 50 per cent. above the adult level. The curve reaches its acme in the almost unexplored period between two and six years and then falls fairly rapidly until the age of twenty years. After this the decrease is extremely gradual.

Just why newborn infants should have such a low metabolism we do not know. It is conceivable that the high metabolism of older children is in part due to the relatively large size of the head, body, and especially the liver. Men with their legs cut off resemble babies in the relative proportions of body and extremities. Two such individuals studied in the calorimeter have been found to have a high metabolism. This would not explain the high metabolism of the boy scouts who have reached the adult proportions although they have not attained adult size. Theorists might go so far as to say that the increased heat production proves in itself an increased thyroid activity in childhood. It is safer for several reasons to ascribe it to some unknown stimulus associated with growth. For the level of metabolism falls as the rate of growth decreases, but rises again in the case of the boy scouts just before the onset of puberty, a period when the rate of growth is once more accelerated. Again, in adult life the nearest approach to the growth of childhood is found in convalescence from acute infectious diseases, and there is a distinct rise in metabolism in the convalescence from typhoid fever.[4 38]

METABOLISM IN DISEASE. The most striking disease from the standpoint of changes in the total metabolism is exophthalmic goitre, and clinicians who pay no attention to the gaseous exchanges neglect the most important phase of this malady. Friedrich Müller first called attention to the high metabolism in Basedow's disease by noting the nitrogen and weight losses of patients taking enough food to maintain normal subjects in nutritive equilibrium. Magnus-Levy [40] [41] found the gaseous exchanges very high in Graves's disease and very low in myxedema.[42] His results have been amply confirmed by Stüve,[43] Hirschlaff,[44] Salomon[45] and others, and by those of us working with the Sage calorimeter.[46] If we group 33 cases of hyperthyroidism studied by other investigators with the 11 studied in New York, we find that the increase in metabolism is strictly proportional to the severity of the clinical symptoms. One fatal case of Hirschlaff's in the last two weeks of life showed an increase of 120 per cent. above the average normal and two severe but nonfatal cases at Bellevue have given results which are 100 per cent. above the normal. In general, it may be said that very severe cases show an increase of 75 per cent. or more, severe cases 50 per cent. or more, moderately severe and mild cases less than 50 per cent., while a few mild, atypical or operated cases may be within normal limits.

This increase in metabolism is the most striking effect of thyroid activity, and it is equalled in no other disease. In cretinism and myxedema the metabolism may be 25 to 50 per cent. below the normal level. Thyroid extract raises the metabolism in these conditions and has a similar though less constant effect on normal men and obesity patients. No other glandular extract yet examined has this property in any significant degree. Many of the symptoms of hyperthyroidism are secondary to the abnormal heat production. The flushed, warm skin and the sweating are physiological methods of dissipating extra heat. The increased appetite and the loss of weight that sometimes occur in spite of this are the results of increased calorific requirements. Part of the tachycardia is certainly due to the greater demands for oxygen.

Most of the investigators who have studied the gaseous exchanges in this disease have used the level of the metabolism as an index of the effect of treatment. This procedure is perfectly logical, and it is particularly desirable to have some purely objective guide to therapeusis in a disease where there is so much psychotherapy on the part of the physician and patient. Previous observers have found no change in the metabolism after the administration of rhadogen,[45] Roentgen rays,[47] and the serum of thyroidectomized animals,[45] but have established a prompt drop after partial thyroidectomy.[45] In the cases observed at Bellevue a fall of 10 or 15 per cent. has resulted from rest alone, and none of the other therapeutic measures tried gave any better results. These included

Beebe's serum, ergotin, and quinin hydrobromate, and finally thyroid residue. But since the two former methods were tried on only one patient it is nor fair to condemn them. With several patients the thyroid arteries were ligated, and it was found that this procedure caused a sharp rise in the metabolism which fell subsequently to its former level. The operative procedure, although very conservatively done under local anesthesia, increases temporarily the activity of the gland. There is as yet no proof that any form of medical treatment or ligation of arteries causes a greater reduction in metabolism than rest in bed. Several important facts have been brought out in regard to the administration of food to Basedow patients. They need large amounts of food with an abundant, though not excessive, protein ration. Von Noorden[49] has warned us against the use of large amounts of protein and especially meat, assuming that it causes a greater rise in heat production in sickness than in health. Pribram and Porges[17] found that after a diet with large amounts of meat the metabolism was slightly increased, but not more so than in normal people. Undeutsch[43] found that the protein of meat causes less stimulation than vegetable proteins. With the Sage calorimeter it has been found that the specific dynamic action of protein and carbohydrate with exophthalmic goitre patients is not appreciably different from the normal, and that there is no significant difference between the effects of meat and the same amount of protein in milk and eggs. It has taken a large amount of work to disprove the hypothesis of a prominent specialist. Still, it is a great relief to know that we need not worry our patients with restrictions on the kinds of proteins they take. The protein ration should contain about 12 to 15 grams of nitrogen a day, which is the amount ordinarily consumed.

The carbohydrates are readily metabolized in spite of the moderate glycosuria found in severe cases. Except in the true cases of diabetes with goitre it is an abnormality of mobilization rather than utilization. One of the severe cases at Bellevue Hospital was able to derive 90 per cent. of his calories from the oxidation of carbohydrates in spite of a marked glycosuria. A severe case of diabetes could not have derived 10 per cent. of his calories from this source, and even a mild case would scarcely have reached the figure of 50 per cent. Goitre patients use up carbohydrates rapidly, and fourteen hours after their last meal are maintaining themselves almost entirely on fat and protein.

In regard to the medical treatment of Graves's disease the calorimeter may be a therapeutic Nihilist, but it is a dietetic enthusiast, and it is also a strong supporter of the belief that mental and physical rest are essential in the treatment of severe cases.

DIABETES MELLITUS. The Harvey Society is fortunate in having, almost every year, a lecture devoted exclusively to the fascinating subject of diabetes mellitus. The respiratory metabolism was discussed last year in a masterly fashion by Joslin,[50] who, with Benedict, in Boston,[1 2 3] has done an enormous amount of work on this subject. During the past year, working in coöperation with Dr. Allen,[51] of the Rockefeller Hospital, it has been possible to study in the greatest detail one particularly severe case of diabetes snatched from coma by the Allen fasting treatment. This case and several others also studied have given such striking confirmation to the views held by Lusk,[52 53 54 55] for many years, that it is impossible to pass the subject by. Lusk was the first to maintain that a patient who was completely diabetic would excrete not only all the ingested carbohydrate but would also turn about half of the protein molecule into sugar and excrete it in the urine. Under these conditions the excess of excreted sugar over ingested would be about three and a half times the nitrogen in the urine: in other words, the D : N ration would be 3.65. Under these circumstances the respiratory quotient would be depressed below that of fat by the incomplete combustion of protein instead of being raised by protein as with normal people. The lowest possible quotient in health is 0.72, and in complete diabetes with the D : N ratio 3.65, Lusk has calculated that the quotient might be depressed to 0.69. One of the severe cases above mentioned with the D : N of 3.5 showed a quotient of 0.697, another with the D : N of 3.1 gave a quotient of 0.692. There was absolutely no evidence of any formation of sugar from fat. The D : N ratio if determined under the proper precautions is certainly the best guide as to the severity of the case.

The effect of the Allen[56] fasting treatment in the severe case most completely studied was to cause a gradual rise in the quotient as the D : N ratio fell and the glycosuria cleared up. After the fast the curious phenomenon mentioned by Joslin[50] was noted. There was a rise in quotient indicating the combustion of carbohydrate from some unknown source. This may be stored glycogen, excess of sugar in blood and tissues, or perhaps it may be due to the oxidation of acetone bodies.

Another effect of the fast was the marked fall in total metabolism. The patient was brought to a condition where his low food requirement could be met by his improved though still damaged metabolic functions. The metabolism was reduced to a point even lower than that reached by normal men fasting a long time.

This brings us to the question of the total metabolism in diabetes, still the subject of controversy. The older investigations by Pettenkofer and Voit,[57] Nehring and Schmoll,[58] Magnus-Levy,[59] Du Bois and Veeder[60] and others indicated only a slight increase in total metabolism. More recently Benedict and Joslin,[1 2 3] who have studied a large number of cases, have maintained that the metabolism averages about 15 per cent. above the normal in severe diabetes, and Rolly[61] and Leimdörfer[62] reached the same conclusion. Lusk[63] has gone over the results obtained by Benedict and Joslin using different normal controls for the purposes of comparison, and has concluded that the metabolism is but slightly increased. An interesting light has been thrown on this subject by the new method of calculating the surface area. It was noted in one severe case of diabetes, studied before the fast at Bellevue Hospital, that the metabolism was 2 per cent. above the average figure according to Meeh's formula, but 8 per cent. below according to the true surface area. Patients with severe diabetes are usually very thin, and in such cases comparisons based on Meeh's formula are untrustworthy. If we recalculate the severe cases of Benedict and Joslin by means of the new height-weight formula we find that the average is about 3 per cent. above the standard figure of 39.7 calories per square meter per hour. The cases studied at Bellevue were all below the normal, but some of them were low on account of fasting. (One patient very recently studied showed a slight increase in metabolism for a few days. His acidosis and also his nitrogen elimination were unusually high.)

TYPHOID FEVER. Typhoid lends itself particularly well to a study of the changes in metabolism which occur in fever. It is more uniform in its course than most fevers, is protracted, is often severe, and is with us every autumn. There are several factors at work in a typhoid patient: (1) toxemia, (2) fever, and (3) more or less starvation. Since the introduction of the Shaffer-Coleman[65] high calory diet this last factor has almost disappeared, leaving a much more satisfactory disease for the patient and for the scientific investigator. The work done on the nitrogen metabolism has been voluminous, and the controversy concerning the toxic destruction of protein is still violent. The respiratory metabolism has been studied by many investigators, notably Kraus,[66] Svenson,[67] Grafe,[68] and Rolly.[69] At Bellevue Hospital 134 observations with the small Benedict apparatus have been made by Coleman and the writer and 61 with the Sage calorimeter.

The total metabolism in typhoid fever shows an increase which is roughly proportional to the rise in temperature. At the height of the fever it averages about 40 per cent. above the normal, but in some cases may be more than 50 per cent. above. Patients who are liberally nourished with the high calory diet of Coleman and Shaffer do not have a greater heat production than patients on low diets. The Sage calorimeter has shown that the specific dynamic action of protein and glucose is much smaller than normal, and in fact almost absent in typhoid fever. The practical application of all this is that typhoid patients need more food than normal men under similar conditions, and that food even in large amounts is well absorbed and does not increase the heat production, as was previously feared. Typhoid patients like all others with high metabolism use up their carbohydrate food and glycogen stores rapidly, and this type of food should be given in large amounts if we do not want the patients to subsist on protein and fat obtained chiefly from their own tissues.

The actual heat production of most of the typhoid patients is between 2000 and 3000 calories a day. Such amounts, as a rule, can be readily administered, and to me personally it hardly seems necessary to give more than 3000 calories a day unless the patient wants it. Dr. Coleman, whose experience is much greater than mine, believes that patients do best on larger amounts, since these alone will prevent the loss of body protein.

A series of careful experiments has been made in which the nitrogen and respiratory metabolism was studied at the same time. Now a normal man can be maintained in nitrogen and weight equilibrium if given a moderate amount of protein and enough calories to cover the heat production as calculated from the basal metabolism, with allowance for food stimulation and muscular activity. It has been possible by means of the Sage calorimeter to determine the actual heat production of a series of typhoid patients. In the adjoining metabolism ward the head nurse, Miss Magill, and her assistants have skilfully administered food in sufficient amount amply to cover the caloric output. Yet the patients have shown distinctly negative nitrogen balances during the febrile period, and in one case for several days after the fever had ended. This is conclusive proof that there is an abnormal destruction of protein in typhoid fever, and the evidence indicates that this is due chiefly to the toxins of the disease. Shaffer and Coleman were able to demonstrate that this toxic destruction could be prevented or masked by the administration of very large amounts of food, particularly carbohydrates. Kocher[30] has recently shown that in fever even with large amounts of food the nitrogen excretion can never be reduced to the low point of 3 to 4 grams a day readily obtained in health.

In the early days of convalescence from typhoid the metabolism is slightly below the normal, then it rises to 15 to 20 per cent. above, apparently as the result of the large amounts of food and the stimulus of growth. In convalescence the specific dynamic action of food is either normal or else greater than normal. We do not care if the heat production at this period be increased and there is no contra-indication from the metabolic standpoint to liberal feeding in convalescence.

The problem of the mechanism of the rise and fall in body temperature in fever has been the subject of much experimentation, and the question can be settled only by a respiration calorimeter. For reasons that cannot be discussed in a short paper the technic is difficult, and there are only 11 of the calorimeter experiments in typhoid which meet the rigid requirements. These indicate that a rising temperature is accompanied by an increasing heat production which outweighs a slightly increasing heat elimination. With a falling temperature the production remains fairly level while the elimination is increased.

ANEMIAS. The question of the oxidative processes in cases of severe anemia is of particular interest. When the hemoglobin content of the blood is greatly reduced it is difficult to see how the tissues can be supplied with enough oxygen, and yet every clinician has seen patients with 20 to 30 per cent. of the normal percentage of hemoglobin who are not dyspneic. How is this possible? The blood volume is not increased enough to account for the compensation, the plasma can carry only small amounts of oxygen, the hemoglobin in anemia does not possess an abnormal power to combine with extra amounts of oxygen. Some experimenters have believed that the oxygen requirement in such patients was lower than normal.

The respiratory metabolism in various types of anemia has been studied by Magnus-Levy,[71] Kraus,[72] Bohland,[73] Thiele and Nehring,[74] Grafe,[75] and six cases of pernicious anemia have been observed in the Sage calorimeter by Meyer and the writer.[76] In few cases examined by investigators I have named was the metabolism below normal. In lymphatic leukemia it was often 50 per cent. above normal, perhaps on account of the abnormal oxidative activity of the white blood cells, perhaps on account of lactic acid formation. In two severe cases of pernicious anemia at Bellevue Hospital with 20 per cent. hemoglobin the metabolism was 24 and 39 per cent. above normal.

The chief compensatory factor in such patients would seem to be an increased cardiac output per minute. It appears also that the blood is more completely robbed of its oxygen in its passage through the capillaries.

CARDIORENAL DISEASE. The previous works on the gaseous exchanges in cardiac and renal disease have not been extensive and have been marred by respiratory quotients which are so low that it has been necessary for the investigators to assume abnormal processes. Peabody, Meyer and Du Bois[77] have studied 16 patients in the calorimeter, a number which is somewhat small when we consider the variations present in these diseases. In general it may be said that mild cases of nephritis and compensated cardiac patients are within normal limits, as are a few severe cases of both diseases. An increase in heat production amounting to 30 to 40 per cent. is found in most of the very dyspneic patients. The cause of the rise may be in part the increased work of respiration and increased labor of the heart, but the chief factors are yet to be discovered.

There is no evidence of profound changes in the intermediary metabolism in cardiac and nephritic dyspnea. Not a single abnormal quotient has been found by the calorimeter. We must remember that the patients with high metabolism use up more food than normal men, and with ordinary diet will suffer from partial starvation. If not given large amounts of carbohydrate in the food they will subsist chiefly on fat and protein derived largely from their own tissues. It is worth while to remember these things when we order the restricted diets which seem necessary in many cases of cardiac and renal disease.

Miscellaneous Conditions. Many other diseases have been studied in various clinics, but it is impossible to discuss them at length. Grafe[78] has found an increase in metabolism in cancer and only a moderate increase in low-grade fevers. Various diseases of the pituitary have been studied by Falta[64] in Vienna, by Means[24] in Boston, and by the Sage staff in Bellevue Hospital.[79] Results are variable and no conclusions can be drawn as to any marked change in the respiratory metabolism except that in acromegaly there is slight but fairly constant rise in heat production. The metabolism of women just before and just after childbirth was studied most carefully by Carpenter and Murlin[80] using one of the calorimeters in Benedict's laboratory. The effect of drugs on the heat production of men has been studied by Loewy,[81] Lindhard[82] and others and important work is now being done on this subject by Edsall[83] and Higgins and Means.[84]

We must not forget that much of our knowledge of the respiratory metabolism in disease is due to the work done on animals and normal men. We need only mention the researches in this country of Lusk, Benedict, Murlin, Carpenter and many others.

General Considerations. We have seen that the respiration calorimeter measures the heat production by the independent methods of direct and indirect calorimetry. The direct method must remain the standard in the long run and any significant and consistent divergence of the indirect method in any particular disease would indicate a marked change in the intermediary metabolism. It would show that the food-stuffs were not broken down to the same end-products with the same liberation of heat as in normal subjects. Such changes in disease have often been considered very seriously, particularly by investigators who, on account of defective technic, have obtained abnormally low quotients. The calorimeter has obtained no such quotients except in severe diabetes, where they are to be expected. The direct and indirect calorimetry have agreed very closely when we consider the technical difficulties in short observations with sick patients. Until a very few years ago no one would have dreamed of trying to make the two methods agree in periods shorter than six hours. At that time the calculations were not even carried out, but if we now go over some of the work in Benedict's laboratory[80] as early as 1911 we find excellent agreement in two-hour subdivisions of four-hour experiments. With the

Cornell calorimeter built by Williams,[9] Lusk has been able to obtain remarkable agreement in periods as short as an hour with dogs and a dwarf. Howland[31] has obtained similar results with babies. When the totals obtained on all the normal controls studied in the Sage calorimeter are compared it is found that the two methods agree within 0.2 of 1 per cent. With the experiments two to three hours long, such as are used with patients, certain technical errors have a tendency to make the direct calorimetry too low, and we find it 2.2 per cent. lower in typhoid fever, 2.8 per cent. in exophthalmic goitre, 2.3 per cent. in diabetes, 3.3 per cent. in anemia, 1.9 per cent. in the group of cardiac and nephritis patients. These divergences are within the limits of technical error; they are so small that we can be certain that the law of conservation of energy holds good in disease and can also be sure that there are no profound and unsuspected changes in the intermediary metabolism. It is not possible to rule out small changes which might be concealed by the limits of technical error. The chief function of the calorimeter has been to show that the principles of indirect calorimetry are correct when applied to disease. Another function is to make it difficult for overenthusiastic theorists to promulgate wild hypotheses.

The results of work with calorimeters and other types of respiration apparatus must build the foundations of our theories of the nutrition of patients. If we desire to administer to any given patient his exact requirement it is necessary to make several experiments on the patient himself. It is very doubtful if the most experienced observer can guess the heat production of a sick man within 20 per cent. Still, it is possible to make rough calculations which will allow the physician to reckon out the caloric requirements of his patients somewhat more exactly than the trained nurse. We can use as a standard the basal requirement of healthy men between the ages of twenty and fifty and add 10 per cent. for the stimulation of food and about 10 per cent. for the usual activity of a patient confined to bed. Under these conditions the food requirement for the day would be 1800 calories for a man of 125 pounds, 2000 calories for 150 pounds, and 2200 calories for a man of 175 pounds. Bearing in mind the numerous factors already discussed we can add the various percentages according to the disease and its severity. If the patients are permitted to get out of bed, or if they are very restless, we must allow for an increase of anywhere between 20 and 100 per cent. during the hours when they are moving about.

Some observers have attempted to determine the total food requirement in disease by observing the intake and output of nitrogen. Such experiments in nitrogen equilibrium must be continued for weeks to give much evidence on this point. The work at Bellevue Hospital in typhoid fever[35] has shown that a negative nitrogen balance may exist when the caloric needs are more than covered by the food.

In many cases the fluctuations of body weight serve as a guide to the nutritive condition of the body. We must not place too much reliance on short observations. Rapid changes in weight are due in great part to changes in the water content of the body. Benedict[3] quotes the case of a football player who lost 14 pounds in a game one hour and ten minutes long. Only one-quarter pound was due to the oxidation of solids, 13¾ pounds was water loss. We are familiar with the retention of large amounts of water in edema and are familiar with the role of salts, but we do not realize the frequency of invisible edema. A diet rich in carbohydrates causes the body to retain considerable amounts of water; a fat diet has the opposite effect.

Many clinicians are in the habit of measuring the fluid intake and urinary output under the impression that they are determining the water balance. Patients in the calorimeter eliminate water through skin and lungs at a rate which varies between ½ and 1 liter a day. The fluids of the diet form but a small part of the water intake. Rennet, a solid food, contains just as much water as milk. Potatoes are 75 per cent. water, tomatoes 94 per cent. An accurate water balance is one of the most difficult problems in experimental metabolism and we must not place too much reliance on changes in weight unless followed for long periods.

In reviewing the subject of metabolism in disease one can see that clinicians too long contented themselves with urinalyses and measurements of intake and output. Now they are thinking in terms of the blood and the fluids which bathe the cells. It is certainly worth while to go one step farther and study more closely the respiratory metabolism which tells of the results of the activities in the tissues themselves.

## REFERENCES.

1. Benedict and Joslin. Metabolism in Diabetes, Carnegie Inst., Washington, 1910, Bull. 136.
2. Benedict and Joslin. Metabolism in Severe Diabetes, ibid., 1912, Bull. 176.
3. Benedict and Joslin. Deutsch. Arch. f. klin. Med., 1913, cxi, 333.
4. Coleman and Du Bois. Arch. Int. Med., 1914, xiv, 168.
5. Atwater and Rosa. Report of the Storrs Agricult. Exp. Station, 1897, p. 212.
6. Langworthy and Milner. Jour. Agricult. Research, 1915, v, 299.
7. Atwater and Benedict. Carnegie Institution of Washington, 1905, Pub. 42.
8. Benedict and Carpenter. Ibid., 1910, Pub. 123.
9. Williams. Jour. Biolog. Chem., 1912, xii, 317.
10. Riche and Soderstrom. Arch. Int. Med., 1915, xv, 805.
11. Carpenter. A Comparison of Methods for Determining the Respiratory Exchange of Man, Carnegie Inst., Washington, 1915, Pub. 216.
12. Benedict, F. G. Am. Jour. Physiol., 1909, xxiv, 345.
13. Benedict, F. G. Deutsch. Arch. f. klin. Med., 1912, cvii, 156.
14. Rubner. Ztschr. f. Biol., 1883, xix, 545.
15. Meeh. Ztschr. f. Biol., 1879, xv, 425.
16. D. Du Bois and E. F. Du Bois. Arch. Int. Med., 1915, xv, 868.

17. D. Du Bois and E. F. Du Bois. Proc. Soc. Exp. Biol. and Med., 1916.
18. Gephart and Du Bois. Arch. Int. Med., 1915, xv, 835.
19. Benedict, Emmes, Roth, and Smith. Jour. Biolog. Chem., 1914, xviii, 139.
20. Benedict and Roth. Ibid., 1915, xx, 231.
21. Benedict and Smith. Ibid., 1915, xx, 243.
22. Benedict and Emmes. Ibid., 1915, xx, 253.
23. Benedict. Ibid., 1915, xx, 263.
24. Means. Jour. Med. Research, 1915, xxxii, 121.
25. Palmer, Means, and Gamble. Jour. Biolog. Chem., 1914, xix, 239.
26. Means. Jour. Biol. Chem., 1915, xxi, 263.
27. Soderstrom, Meyer, and Du Bois. In press.
28. Rubner. Gesetze des Energieverbrauch's, 1902, Leipzig, Deutsche.
29. Lusk. Animal Calorimetry Papers. Paper XI, Jour. Biolog. Chem., and previous papers of series in same journal.
30. Magnus-Levy and Falk. Arch. f. Anat. and Physiol., 1899, Suppl. 315.
31. Howland. Ztschr. f. Physiolog. Chem., 1911, lxxiv, 1.
32. Benedict and Talbot. Carnegie Inst., Washington, 1914, Pub. No. 201.
33. Benedict and Talbot. Am. Jour. Dis. Child., 1914, viii, 1.
34. Benedict and Talbot. Carnegie Inst., Washington, Pub. No. 201.
35. Murlin and Hoobler. Am. Jour. Dis. Child., 1915, ix, 81.
36. Bailey and Murlin. Am. Jour. Obstet. and Dis. of Women and Child., 1915, lxxi, 1.
37. Du Bois. In press.
38. Coleman and Du Bois. Arch. Int. Med., 1915, xv, 887.
39. Müller, Fr. Deutsch. Arch. f. klin. Med., 1893, li, 335.
40. Magnus-Levy. Berl. klin. Wchnschr., 1895, xxxii, 650.
41. Magnus-Levy. Ztschr. f. klin. Med., 1897, xxxiii, 269.
42. Magnus-Levy. Ztschr. f. klin. Med., 1904, lii, 201.
43. Stüve. Fest. Städt. Krankenh. Frankfurt a. M., 1896.
44. Hirschlaff. Ztschr. klin. Med., 1899, xxxvi, 200.
45. Salomon. Berl. klin. Wchnschr., 1904, xxiv, 635.
46. Du Bois. In press.
47. Pribram and Porges. Wein. klin. Wchnschr., 1908, xxi, 1584.
48. Undeutsch. Exp. Gaswechseluntersuch. bei Marb. Basedowii, Inaug. Dissert., 1913, Leipzig.
49. Von Noorden. New Aspects of Diabetes, New York, E. B. Treat & Co., 1912, p. 20.
50. Joslin. Arch. Int. Med., 1915, xvi, 693.
51. Allen and Du Bois. In press.
52. Reilly, Nolan, and Lusk. Am. Jour. Physiol., 1898, i, 395.
53. Mandel and Lusk. Deutsch. Arch. f. klin. Med., 1904, lxxxi, 472.
54. Lusk. Arch. Int. Med., 1909, iii, 1; also the Harvey Lectures, 1908–1909.
55. Lusk. Arch. Int. Med., 1915, xv, 939.
56. Allen, F. M. Boston Med. and Surg. Jour., 1915, vol. i.
57. Pettenkofer and Voit. Ztschr. f. Biol., 1867, iii, 380.
58. Nehring and Schmoll. Ztschr. f. klin. Med., 1897, xxxi, 59.
59. Magnus-Levy. Ztschr. f. klin. Med., 1905, lvi, 83.
60. Du Bois and Veeder. Arch. Int. Med., 1910, v, 37.
61. Rolly. Deutsch. Arch. f. klin. Med., 1912, cv, 494.
62. Leimdörfer. Biochem. Ztschr., 1912, xl, 326.
63. Lusk. Science, 1911, xxxiii, 433; also Jour. Biolog. Chem., Animal Calorimetry, 1915, xi, xx, 598.
64. Falta. Die Erkrankungen der Blutdrüsen, Berlin, Springer, 1913, p. 440.
65. Shaffer and Coleman. Arch. Int. Med., 1909, iv, 538.
66. Kraus. Ztschr. f. klin. Med., 1891, xviii, 160.
67. Svensen. Ibid., 1901, xliii, 86.
68. Grafe. Deutsch. Arch. f. klin. Med., 1911, ci, 209.
69. Rolly. Ibid., 1911, ciii, 93.
70. Kocher. Deutsch. Arch. f. klin. Med., 1914, cxv, 82.
71. Magnus-Levy. Ztschr. f. klin. Med., 1906, lx, 179.
72. Kraus. Ztschr. f. klin. Med., 1893, xxii, 458.
73. Bohland. Berl. klin. Wchschnr., 1893, xviii, 417.
74. Thiele and Nehring. Ztschr. f. klin. Med., 1896, xxx, 41.
75. Grafe. Deutsch. Arch. f. klin. Med., 1911, cii, 406.
76. Meyer and Du Bois. In press.

77. Peabody, Meyer and Du Bois. In press.
78. Grafe. Deutsch. med. Wchnschr., 1914, xl, 518.
79. Du Bois. Jour. Am. Med. Assn., 1914, lxiii, 827.
80. Carpenter and Murlin. Arch. Int. Med., 1911, vii, 184.
81. Loewy. Arch. f. d. gesammte Physiol., 1890, xlvii, 601.
82. Lindhard. Jour. Physiol., 1911, xlii, 337.
83. Edsall and Means. Arch. Int. Med., 1914, xiv, 897.
84. Higgins and Means. Jour. Pharm. and Exp. Ther., 1915, vii, 1.
85. Lusk. Animal Calorimetry, Papers 1 to 12, Jour. Biol. Chem., 1912-1915.

---

# A NEW CLASSIFICATION OF NEOPLASMS AND ITS CLINICAL VALUE.[1]

By Wm. Carpenter MacCarty, M.D.,

MAYO CLINIC, ROCHESTER, MINNESOTA.

I TAKE the liberty of presenting a new classification of neoplasms[2] for the following reasons:

1. It has been clearly demonstrated that carcinoma in three different organs arises from the regenerative cells of the parenchyma of the organs and not from the parenchyma of these organs (breast, skin and prostate).[3]

2. It has been definitely established that cancer cells of different organs of different germinal layer origin are often morphologically indistinguishable.[4]

3. It has been definitely shown that even the best pathologists cannot always differentiate carcinoma from sarcoma, the cells being often morphologically indistinguishable.

4. It may be seen from the writings of many authorities who classify tumors that their classifications are based on the histogenesis of tissues, and that many of these authorities express dissatisfaction with this basis of classification and apologetically accept it as the best, under the existing state of our knowledge.[5]

---

[1] Read before the Section on Pathology and Physiology of the Sixty-sixth Annual Session of the American Medical Association, San Francisco, June, 1915.

[2] This brief statement of a biological conception of neoplastic cytological processes serves merely as a preliminary report and is presented at the present time for the purpose of stimulating pathologists and clinicians to study their early neoplasms and chronic inflammatory conditions in the light of the process of tissue regeneration. It also serves to point the way to the standardization of histological and cytological facts with clinical experience.

[3] MacCarty, W. C., Carcinoma of the Breast, Old Dominion Jour. Med. and Surg., 1911, xii, 189, and Tr. South. Surg. Assn., 1910, xxiii. The Histogenesis of Cancer of the Breast, Surg., Gynec. and Obst., 1913, xvii, 441. Clinical Suggestions Based upon a Study of Primary, Secondary (Carcinoma?), and Tertiary (Carcinoma) Epithelial Hyperplasia in the Breast, Surg., Gynec. and Obst., 1914, xviii, 281. The Biological Position of the Carcinoma Cell, Collected Papers of the Mayo Clinic, 1914, vi, 594. Precancerous Conditions, Jour. Iowa State Med. Soc., 1914, iv, 1.

[4] MacCarty, W. C., Notes on the Irregularity and Similarity of Cancer Cells, Collected Papers of the Mayo Clinic, 1914, vi, 600.

[5] Adami, J. G., Principles of Pathology, Philadelphia, Lea & Febiger, 1909, i. Borst, M., Die Lehre von den Geschwülsten, Wiesbaden, Bergman, 1902. Councilman, W. T.,